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Gone to Pot: The Association Between Cannabis and Psychosis

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Cannabis, or marijuana, has been consumed by humans for centuries and remains one of the most widely and commonly used illicit substances. Recently, there has been renewed interest in the association between cannabis use and psychosis. The purpose of this article is to review the evidence supporting and refuting the association between cannabis exposure and psychotic disorders, including schizophrenia.

As far back as 1845, Dr. Jacques- Joseph Moreau de Tours described psychotic phenomena with hashish use as:

[A]cute psychotic reactions, generally lasting but a few hours, but occasionally as long as a week; the reaction seemed doserelated and its main features included paranoid ideation, illusions, hallucinations, delusions, depersonalization, confusion, restlessness and excitement. There can be delirium, disorientation and marked clouding of consciousness.

In 1964, Gaoni and Mechoulam identified -9 tetrahydrocannabinol (-9-THC) as the principal psychoactive ingredient of cannabis.

The identification and cloning of a brain cannabinoid receptor (CB-1) in 1990 provided a jump start to renewed research on cannabinoids (Matsuda et al., 1990). Most of the psychoactive effects of cannabis are believed to be mediated by CB-1 receptors where -9-THC is a modest affinity (K_i=35 nmol to 80 nmol) low intrinsic activity partial agonist. A peripheral receptor later named CB-2 was identified in splenic tissue (Munro et al., 1993). Recent evidence suggests the presence of other brain cannabinoid receptors. The presence of cannabinoid receptors led to the logical search for endogenous cannabinoid receptor ligands, culminating in the discovery of anandamide and 2-arachidonoyl glycerol, two of the better known endogenous cannabinoids or endocannabinoids. Cannabinoid-1 receptors are distributed with high density in the cerebral cortex, particularly the frontal regions, basal ganglia, hippocampus, anterior cingulate cortex and cerebellum (Glass et al., 1997; Herkenham et al., 1990), brain regions that are relevant to their known effects. Further, these are also regions that have been implicated in the putative neural circuitry of psychosis. The primary effect of cannabinoids is the modulation of neurotransmitter release via activation of presynaptic CB1-Rs (reviewed in Demuth and Molleman, in press; Freund et al., 2003). Of note, some of these neurotransmitters (eg, dopamine and glutamate) have been implicated in the pathophysiology of psychosis.

The effects of herbal cannabis are a composite of a number of cannabinoid compounds, terpenoids and flavonoids. Thus, cannabidiol, a constituent of herbal cannabis, may offset some -9-THC effects (Zuardi et al., 1995). The ratio of the constituents of herbal cannabis varies, and this may result in important differences in its net effect.

Emerging data suggest an association between cannabis exposure and the development of schizophrenia (Table). Interest in the association between cannabis and schizophrenia received a major boost from the Swedish Conscript study, a large historical, longitudinal cohort study of all Swedes conscripted in 1969-1970 (Andreasson et al., 1987). Since Sweden mandates military service, 97% of males aged 18 to 20 years were included. Individuals who at age 18 reported having used cannabis >50 times were six times more likely than nonusers to have been diagnosed with schizophrenia in the ensuing 15 years. Adjusting for other relevant risk factors, including psychiatric diagnosis other than psychosis at conscription, reduced but did not eliminate the higher risk (odds ratio [OR]=2.3) of schizophrenia conferred by cannabis use.

A reanalysis and extension of the same Swedish conscript cohort reconfirmed that those who were heavy cannabis users by the age of 18 were 6.7 times more likely than nonusers to be hospitalized for schizophrenia 27 years later (Zammit et al., 2002). The OR for cannabis use and schizophrenia remained significant (1.2), albeit lower than in the original study, despite adjusting for a number of confounds, including low IQ and stimulant use. Further, the finding of an increased risk of schizophrenia conferred by cannabis use persisted after controlling for the possibility that cannabis use was a consequence of prodromal manifestations of psychosis.

Several recent prospective cohort studies complement studies using a historical approach. In a general population birth cohort study of 1,037 people born in Dunedin, New Zealand, and followed through age 26, individuals using cannabis at ages 15 and 18, compared to nonusers, had higher rates of both psychotic symptoms at age 26 (even after controlling for psychotic symptoms) and schizophreniform disorder predating the onset of cannabis use (Arseneault et al., 2002). Similarly, cohort studies from elsewhere have also reported a dose-response relationship in the increased risk of psychosis with cannabis exposure (Ferdinand et al., 2005a; Fergusson et al., 2003; Henquet et al., 2005; Stefanis et al., 2004; van Os et al., 2002; Weiser et al., 2002). Several studies of patients during their first-break psychosis suggested that cannabis use precedes or is coincident with the first psychotic break in patients with schizophrenia (Allebeck et al., 1993; Hambrecht and Hafner, 2000).

Are these data sufficient to constitute a causal relationship? And if so, how strong is the association? Temporality, strength, association, direction, dose-response or biological gradient, consistency, specificity, coherence, experimental evidence, and plausibility are some of the criteria that have been used to establish disease causality (Aiello and Larson, 2002).

Several studies reviewed here provided evidence of a dose-response relationship between cannabis exposure and the risk of psychosis. Most studies also provided evidence of direction by showing that the association between cannabis use and psychosis persists even after controlling for many potential confounding variables such as IQ, education, urbanicity, marital status and previous psychotic symptoms. With regard to temporality, several studies suggested that cannabis use precedes or coincides with the onset of psychosis. Further, there is also evidence that cannabis use may be associated with a lower age of schizophrenia onset (Green et al., 2004; Linszen et al., 1994). There is evidence for both the specificity of exposure (i.e., cannabis [Arseneault et al., 2002; Ferdinand et al., 2005a, 2005b; Zammit et al., 2002]) and specificity of the outcome (i.e., psychosis [Arseneault et al., 2002; Stefanis et al., 2004]). Experimental evidence from laboratory studies suggested that cannabinoids can induce transient short-lived psychosis in healthy individuals (DSouza et al., 2004; Leweke et al., 2000). Further,

relative to controls, patients with schizophrenia have been shown to be more vulnerable to the psychotomimetic effects of -9-THC (DSouza et al., 2005). While it is out of the scope of this review, the interactions between cannabinoid receptor function and dopamine, glutamate and -aminobutyric acid receptor function provide potential mechanisms by which cannabis may cause psychosis (as reviewed in DSouza et al., 2004, 2005).

One of the most obvious genetic risk factors for psychosis is a family history of psychosis. In a case-control study, cannabis users admitted for schizophrenia had a significantly greater familial risk of schizophrenia than patients with schizophrenia without cannabis use (McGuire et al., 1995). Consistent with these findings, data from the Edinburgh High Risk project showed that frequent cannabis use conferred a sixfold higher risk of schizophrenia in individuals with a family history of schizophrenia (Miller et al., 2001). Recently, a polymorphism of the catechol-O-methyltransferase gene has been reported to modulate the risk of schizophrenia conferred by cannabis (Caspi et al., 2005).

Emerging findings from postmortem (Dean et al., 2001; Zavitsanou et al., 2004), neurochemical (Leweke et al., 1999) and genetic (Ujike et al., 2002) studies suggested cannabinoid receptor system dysfunction contributes to the pathophysiology of schizophrenia. Thus, it is possible that cannabinoid receptor dysfunction is the substrate that links cannabis exposure and psychosis.

Finally, if cannabis causes psychosis in and of itself, then one would expect that any increase in the rates of cannabis use would be associated with increased rates of psychosis. However, in some areas where cannabis use has clearly increased (e.g., Australia), there has not been a commensurate increase in the rate of psychotic disorders (Degenhardt et al., 2003). Further, one might also expect that if the age of initiation of cannabis use decreases, there should also be a decrease in the age of onset of psychotic disorders. We are unaware of such evidence.

In conclusion, there is evidence for an association between cannabis and psychosis. It is clear that cannabinoids can cause acute transient psychotic symptoms or an acute psychosis. Also it is clear that cannabis can exacerbate psychosis in individuals with an established psychotic disorder. However, whether cannabis causes a persistent de novo psychosis independent of any other risk factors is not supported by the existing literature. More likely, cannabis is a component cause that interacts with other factors (e.g., genetic risk) to induce psychosis.

Nevertheless, in the absence of known causes of schizophrenia, the role of component causes such as cannabis use remains important and warrants further study. Finally, studying the role of exogenous cannabinoids in the development of psychosis will need to be complemented by further studying a possible role of endocannabinoid dysfunction in the pathophysiology of psychosis.

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